II. Remarks

A. Status of the Claims

Claims 1, 21-25, 41, and 42 have been amended without prejudice or admission for clarity. Applicants submit that support for these amendments can be found, e.g., in the original abstract, and on page 21, lines 19-21, of the original specification.

New claims 46 and 47 have been added. Applicants submit that support for new claims 46 and 47 can be found, e.g., on page 28, lines 29-33, of the original specification.

Claims 2, 4-7, 11, 28, and 33-34 were previously cancelled without prejudice or admission.

Claims 1, 3, 8-10, 12-27, 29-32, and 35-47 are currently pending.

It is respectfully submitted that no new matter has been added by virtue of the present amendments.

B. Claim Rejection Under 35 U.S.C. § 103(a)

In the Office Action, claims 1, 3, 8-10, 12-27, 29-32, and 35-45 were rejected under 35 U.S.C. § 103(a) over the combination of Nutt et al. (Clinical Pharmacology and Therapeutics, Vol. 15, Number 2, pp. 156-166), Mayer et al. (U.S. 5,556,838), Ockert (U.S. 5,376,662) and European Patent No. 0 193 355.

The rejection is respectfully traversed.

Independent claims 1 and 41 are directed, in part, to an oral dosage form comprising a combination of an opioid agonist, acetaminophen and an opioid antagonist, wherein a ratio of the opioid antagonist to the opioid agonist to the acetaminophen is such that

(i) the combination is analgesically effective when the combination is administered orally,

(ii) is aversive in physically dependent human subjects when administered orally; and

(iii) maintains an analgesic effect but does not increase analgesic efficacy of the opioid agonist together with the acetaminophen, relative to when the opioid agonist and the acetaminophen are administered orally without said opioid antagonist.

It is respectfully submitted that the combination of the cited references does not provide a reason to combine the individual components of the cited references in the manner suggested by the Examiner and to formulate a dosage form as recited in independent claims 1 and 41. It is further submitted that, even if the references were properly combinable (a position which is traversed), the combination of the cited references would still not render independent claims 1 and 41 obvious, because the combination of the cited references does not teach or suggest the ratios recited in the claims 1 and 41.

In response to the Examiner's statement on page 3 of the Office Action that "[t]he primary reference teaches that the mixture has significantly less miotic, behavioral and subjective effect than methadone alone," Applicants note that the portion of Nut et al. believed to be relied upon by the Examiner states:

> **By the parenteral route**, the mixtures have significantly less miotic, behavioral, and subjective effects than methadone alone ...

Nutt et al., Abstract (emphasis added).

Applicants respectfully submit that, Nut et al. state on page 165, right column, first full paragraph, that "... by the oral route ...[the methadone-naloxone mixture described therein] ... is **indistinguishable** from methadone alone" (emphasis added). Applicants therefore submit that Nut et al. (alone or in combination with the cited references) would not have motivated the skilled person to formulate an oral dosage form which "is **aversive** in physically dependent human subjects when administered **orally**" as recited in independent claims 1 and 41.

In response to the Examiner's reliance on Mayer et al., Applicants note that the Mayer et al. is directed in part to "a method of **alleviating** withdrawal symptoms in a mammal" (column 2, lines 23-33), and states that, e.g., that naloxone (an opioid antagonist) produces withdrawal symptoms (column 7, lines 23-26). Applicants therefore submit that Mayer et al. (alone or in combination with the cited references) would not have motivated the skilled person to formulate an oral dosage form comprising "an opioid antagonist, and which "is aversive in physically dependent human subjects when administered orally" as recited in independent claims 1 and 41.

In response to the Examiner's reliance on the Ockert reference, Applicants note that the Ockert reference is directed in part to "local administration of naloxone at or near the nerve trauma site" (column 2 lines 35-48), and states in part that "[n]aloxone and other opiate-antagonists competitively **antagonize** both exogenous opiates (such as heroine or morphine) and endogenous opioids (such as B-endorphin, enkephalins, and dynorphin at both peripheral and central nerve opiate receptors)." Column 4, lines 8-12. Applicants therefore submit that the Ockert reference (alone or in combination with the cited references) would not have motivated the skilled person to combine an opioid agonist and an opioid antagonist in a dosage form which "is aversive in physically

dependent human subjects when administered orally" as recited in independent claims 1 and 41.

For the foregoing reasons, Applicants submit that a dosage form comprising the combination of an opioid agonist, acetaminophen and an opioid antagonist recited in independent claims 1 and 41 is not rendered obvious by the cited references.

With further regard to new claims 46 and 47, Applicants submit that the combination of the cited references does not teach or suggest a dosage form "consisting of the opioid agonist, the acetaminophen, the opioid antagonist, and one or more pharmaceutically acceptable inert excipients," at the very least because fluoxetine, norfluoxetene or salts thereof of European patent No. 0 193 355 and the NMDA receptor blockers of Mayer et al. are excluded from such dosage form, by virtue of the "consisting of" language.

Withdrawal of the rejection is respectfully requested.

III. Conclusion

An early and favorable action on the merits is earnestly solicited. According to currently recommended Patent Office policy, the Examiner is specifically authorized to contact the undersigned by telephone in the event that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,
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